CLAIMS

1. A method for the screening, (differential) diagnosis and/or prognosis in a mammal of Alzheimer's disease, frontotemporal dementia, dementia with Lewy bodies, vascular dementia and/or depression, for identifying a mammal at risk of developing Alzheimer's disease, frontotemporal dementia, dementia with Lewy bodies, vascular dementia and/or depression, or for monitoring the effect of therapy administered to a mammal having Alzheimer's disease, frontotemporal dementia, dementia with Lewy bodies, vascular dementia and/or depression, said method comprising the following steps:

   (a) detecting, in said mammal, the level of at least one of the following proteins: Apo E, α-1-antitrypsin, α-1-β glycoprotein, antithrombin III, Apo A-I, Apo A-IV, Apo J, gelsolin, haptoglobin, hemopexin, Ig α-1 chain C region (heavy), kininogen, prostaglandin-H2 D-isomerase, transthyretin, vitamin D-binding protein, Zn-α-2-glycoprotein, or of an isoform thereof; and

   (b) comparing the level of said at least one protein or protein isoform detected in step (a) with a range of levels previously defined as characteristic for mammals suffering from AD, with a range of levels previously defined as characteristic for mammals suffering from FTD, with a range of levels previously defined as characteristic for mammals suffering from DLB, with a range of levels previously defined as characteristic for mammals suffering from VAD, with a range of levels previously defined as characteristic for mammals suffering from depression and with a range of levels previously defined as characteristic for control mammals; and

   (c) concluding from the comparison in step (b) whether the mammal is suffering from Alzheimer's disease, frontotemporal dementia, dementia with Lewy bodies, vascular dementia and/or depression, whereby a level of said at least one protein or protein isoform in a range previously defined as characteristic for mammals suffering from AD is an indication that said mammal is suffering from AD; and whereby a level of said at least one protein or protein isoform in a range previously defined as characteristic for mammals suffering from FTD

is an indication that said mammal is suffering from FTD; and whereby a level of said at least one protein or protein isoform in a range previously defined as characteristic for mammals suffering from DLB is an indication that said mammal is suffering from DLB; and whereby a level of said at least one protein or protein isoform in a range previously defined as characteristic for mammals suffering from VAD is an indication that said mammal is suffering from VAD; and whereby a level of said at least one protein or protein isoform in a range previously defined as characteristic for mammals suffering from depression is an indication that said mammal is suffering from depression.

2. The method according to claim 1, for the screening, diagnosis and/or prognosis in a mammal of Alzheimer's disease, frontotemporal dementia, dementia with Lewy bodies, vascular dementia and/or depression, for identifying a mammal at risk of developing Alzheimer's disease, frontotemporal dementia, dementia with Lewy bodies, vascular dementia and/or depression, or for monitoring the effect of therapy administered to a mammal having Alzheimer's disease, frontotemporal dementia, dementia with Lewy bodies, vascular dementia and/or depression, said method comprising the following steps:

(a) detecting, in said mammal, the level of at least one of the following proteins: Apo E, α-1-antitrypsin, α-1-β glycoprotein, antithrombin III, Apo A-I, Apo A-IV, Apo J, gelsolin, haptoglobin, hemopexin, Ig α-1 chain C region (heavy), kininogen, prostaglandin-H2 D-isomerase, transthyretin, vitamin D-binding protein, Zn-α-2-glycoprotein, or of an isoform thereof; and

(b) comparing the level of said at least one protein or protein isoform detected in step (a) with the level of said at least one protein or protein isoform in a control mammal; and

(c) concluding from the comparison in step (b) whether the mammal is suffering from Alzheimer's disease, frontotemporal dementia, dementia with Lewy bodies, vascular dementia and/or depression, an altered level of said at least one protein or protein isoform compared to said level in a control mammal

being an indication of the mammal suffering from Alzheimer's disease, frontotemporal dementia, dementia with Lewy bodies, vascular dementia and/or depression.

3. The method according to claim 1, for the differential diagnosis in a mammal of Alzheimer's disease, frontotemporal dementia, dementia with Lewy bodies, vascular dementia and/or depression, said method comprising the following steps:

(a) detecting, in said mammal, the level of at least one of the following proteins: Apo E, α-1-antitrypsin, α-1-β glycoprotein, antithrombin III, Apo A-I, Apo A-IV, Apo J, gelsolin, haptoglobin, hemopexin, Ig α-1 chain C region (heavy), kininogen, prostaglandin-H2 D-isomerase, transthyretin, vitamin D-binding protein, Zn-α-2-glycoprotein, or of an isoform thereof; and

(b) comparing the level of said at least one protein or protein isoform detected in step (a) with the level of said at least one protein or protein isoform in a mammal suffering from another neurological disease.

(c) concluding from the comparison in step (b) whether the mammal is suffering from Alzheimer's disease, frontotemporal dementia, dementia with Lewy bodies, vascular dementia and/or depression.

4. The method according to any of claims 1 to 3, further characterized that the level of at least one of the following neurological disease-associated protein isoforms is detected (Table 2; Table 3; Table 4; Table 6):

- Apo E: NPI 11, NPI 34, NPI 35, NPI 41, NPI 52, NPI 60, NPI 66, NPI 72, NPI 73, NPI 74, NPI 75, NPI 76m, NPI 77;
- α-1-antitrypsin: NPI 1, NPI 42, NPI 43, NPI 44, NPI 59;
- α-1-β glycoprotein: NPI 2, NPI 3, NPI 31, NPI 48;
- Antithrombin-III: NPI 4;
- Apo A-I: NPI 5, NPI 6, NPI 7, NPI 37, NPI 69, NPI 70, NPI 71;
- Apo A-IV: NPI 8, NPI 9, NPI 10;
- Apo J: NPI 12, NPI 13, NPI 14, NPI 15, NPI 16;

- Gelsolin: NPI 17;
- Haptoglobin: NPI 18;
- Hemopexin: NPI 19, NPI 20;
- Ig α-1 chain C region (heavy): NPI 21, NPI 22;
- Kininogen: NPI 23;
- Prostaglandin-H2 D-isomerase: NPI 24, NPI 25;
- Transthyretin: NPI 26, NPI 27, NPI 28m;
- Vitamin D-binding protein: NPI 29, NPI 30;
- Zn-α-2-glycoprotein: NPI 33;
- NPI 32, NPI 36, NPI 38, NPI 39, NPI 40, NPI 45, NPI 46, NPI 47, NPI 49, NPI 50, NPI 51, NPI 53, NPI 54, NPI 55, NPI 56, NPI 57, NPI 58, NPI 61, NPI 62, NPI 63, NPI 64, NPI 65, NPI 67, NPI 68.

5. The method according to claim 2, for the screening, diagnosis or prognosis in a mammal of Alzheimer's disease, for identifying a mammal at risk of developing Alzheimer's disease, or for monitoring the effect of therapy administered to a mammal having Alzheimer's disease, said method comprising the following steps:

(a) detecting, in said mammal, the level of at least one of the following protein isoforms (Table 2): NPI 1, NPI 16, NPI 25;

(b) comparing the level of said at least one protein isoform detected in step (a) with the level of said at least one protein isoform in a control mammal; and

(c) concluding from the comparison in step (b) whether the mammal is suffering from Alzheimer's disease, a decreased level of said at least one protein isoform compared to the level of said at least one protein isoform in a control mammal being an indication of the mammal suffering from Alzheimer's disease.

6. The method according to claim 2, for the screening, diagnosis or prognosis in a mammal of frontotemporal dementia, for identifying a mammal at risk of developing frontotemporal dementia, or for monitoring the effect of therapy

administered to a mammal having frontotemporal dementia, said method comprising the following steps:

(a) detecting, in said mammal, the level of at least one of the following protein isoforms (Table 2): NPI 5, NPI 6, NPI 12, NPI 17, NPI 24;

(b) comparing the level of said at least one protein isoform detected in step (a) with the level of said at least one protein isoform in a control mammal; and

(c) concluding from the comparison in step (b) whether the mammal is suffering from frontotemporal dementia, a decreased level of said at least one protein isoform compared to the level of said at least one protein isoform in a control mammal being an indication of the mammal suffering from frontotemporal dementia.

7. The method according to claim 2, for the screening, diagnosis or prognosis in a mammal of frontotemporal dementia, for identifying a mammal at risk of developing frontotemporal dementia, or for monitoring the effect of therapy administered to a mammal having frontotemporal dementia, said method comprising the following steps:

(a) detecting, in said mammal, the level of at least one of the following protein isoforms (Table 2): NPI 4, NPI 8, NPI 9, NPI 10, NPI 18, NPI 19, NPI 20, NPI 22, NPI 23, NPI 28m, NPI 70;

(b) comparing the level of said at least one protein isoform detected in step (a) with the level of said at least one protein isoform in a control mammal; and

(c) concluding from the comparison in step (b) whether the mammal is suffering from frontotemporal dementia, an increased level of said at least one protein isoform compared to the level of said at least one protein isoform in a control mammal being an indication of the mammal suffering from frontotemporal dementia.

8. The method according to claim 3, for the differential diagnosis in a mammal of Alzheimer's disease versus frontotemporal dementia, said method comprising the following steps:

(a) detecting, in said mammal, the level of at least one of the following protein isoforms (Table 2): NPI 5, NPI 6, NPI 26;

(b) comparing the level of said at least one protein isoform detected in step (a) with a previously defined cut-off value suitable for differentiating mammals suffering from AD versus mammals suffering from FTD; and

(c) concluding from the comparison in step (b) whether the mammal is suffering from AD or from FTD, whereby a level of said at least one protein isoform above the cut-off value being an indication of the mammal suffering from Alzheimer's disease; and whereby a level of said at least one protein isoform below the cut-off value being an indication of the mammal suffering from FTD.

9. The method according to claim 3, for the differential diagnosis in a mammal of Alzheimer's disease versus frontotemporal dementia, said method comprising the following steps:

(a) detecting, in said mammal, the level of at least one of the following protein isoforms (Table 2): NPI 2, NPI 3, NPI 7, NPI 8, NPI 9, NPI 11, NPI 13, NPI 14, NPI 15, NPI 16, NPI 21, NPI 22, NPI 25, NPI 27, NPI 28m, NPI 29, NPI 30, NPI 69, NPI 71;

(b) comparing the level of said at least one protein isoform detected in step (a) with a previously defined cut-off value suitable for differentiating mammals suffering from AD versus mammals suffering from FTD; and

(c) concluding from the comparison in step (b) whether the mammal is suffering from AD or from FTD, whereby a level of said at least one protein isoform below the cut-off value being an indication of the mammal suffering from

Alzheimer's disease; and whereby a level of said at least one protein isoform above the cut-off value being an indication of said mammal suffering from FTD.

10. The method according to claim 3, for the differential diagnosis in a mammal of Alzheimer's disease versus depression, said method comprising the following steps:

(a) detecting, in said mammal, the level of at least one of the following protein isoforms (Table 2; Table 6): NPI 6, NPI 12, NPI 23, NPI 31, NPI 32, NPI 33, NPI 34, NPI 35, NPI 36, NPI 37, NPI 38, NPI 40, NPI 41, NPI 42, NPI 43, NPI 44, NPI 45, NPI 46, NPI 47, NPI 48, NPI 51, NPI 52, NPI 53, NPI 54, NPI 55, NPI 56, NPI 58, NPI 59, NPI 60, NPI 61, NPI 63, NPI 68, NPI 69;

(b) comparing the level of said at least one protein isoform detected in step (a) with a previously defined cut-off value suitable for differentiating mammals suffering from AD versus mammals suffering from depression; and

(c) concluding from the comparison in step (b) whether the mammal is suffering from Alzheimer's disease or from depression, whereby a level of said at least one protein isoform below the cut-off value being an indication of the mammal suffering from Alzheimer's disease; and whereby a level of said at least one protein isoform above the cut-off value being an indication of said mammal suffering from depression.

11. The method according to claim 3, for the differential diagnosis in a mammal of Alzheimer's disease versus depression, said method comprising the following steps:

(a) detecting, in said mammal, the level of at least one of the following protein isoforms (Table 2; Table 6): NPI 39, NPI 49, NPI 50, NPI 57, NPI 62, NPI 64, NPI 65, NPI 66, NPI 67;

(b) comparing the level of said at least one protein isoform detected in step (a) with a previously defined cut-off value suitable for differentiating mammals suffering from AD versus mammals suffering from depression; and

(c) concluding from the comparison in step (b) whether the mammal is suffering from Alzheimer's disease or from depression, whereby a level of said at least one protein isoform above the cut-off value being an indication of the mammal suffering from Alzheimer's disease; and whereby a level of said at least one protein isoform below the cut-off value being an indication of said mammal suffering from depression.

12. The method according to claim 3, for the differential diagnosis in a mammal of Alzheimer's disease versus vascular dementia, said method comprising the following steps:

(a) detecting, in said mammal, the level of at least one of the following protein isoforms (Table 2): NPI 7, NPI 74, NPI 76m;

(b) comparing the level of said at least one protein isoform detected in step (a) with a previously defined cut-off value suitable for the differentiating mammals suffering from AD versus mammals suffering from VAD; and

(c) concluding from the comparison in step (b) whether the mammal is suffering from Alzheimer's disease or from VAD, whereby a level of said at least one protein isoform below the cut-off value being an indication of the mammal suffering from Alzheimer's disease; and whereby a level of said at least one protein isoform above the cut-off value being an indication of said mammal suffering from VAD.

13. The method according to claim 3, for the differential diagnosis in a mammal of Alzheimer's disease versus vascular dementia, said method comprising the following steps:

(a) detecting, in said mammal, the level of the following protein isoform (Table 2): NPI 5;

(b) comparing the level of said protein isoform detected in step (a) with a previously defined cut-off value suitable for differentiating mammals suffering from AD versus mammals suffering from VAD; and

(c) concluding from the comparison in step (b) whether the mammal is suffering from Alzheimer's disease or from VAD, whereby a level of said protein isoform above the cut-off value being an indication of the mammal suffering from Alzheimer's disease; and whereby a level of said protein isoform below the cut-off value being an indication of said mammal suffering from VAD.

14. The method according to any of claims 1 to 13, further characterized that said method is carried out *in vitro*, on a sample obtained from said mammal.

15. The method according to claim 14, further characterized that said sample is taken from the cerebrospinal fluid, plasma or serum of said mammal.

16. The method according to any of claims 1 to 15, characterized in that the level of protein or protein isoform is detected by isoelectric focusing followed by sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE).

17. The method according to any of claims 1 to 15, characterized in that the level of protein or protein isoform is detected by an immunoassay.

18. The method according to claim 17, further characterized that the detection of the level of protein or protein isoform comprises:

(a) contacting the protein or protein isoform with an antibody that specifically recognizes the protein or protein isoform under conditions being suitable for producing an antigen-antibody complex; and

(b) detecting the immunological binding that has occurred between the antibody and the protein or protein isoform.

19. A composition comprising at least one of the following isolated protein isoforms associated with Alzheimer's disease, frontotemporal dementia, dementia with Lewy bodies, vascular dementia and/or depression:

- Apo E: NPI 11, NPI 34, NPI 35, NPI 41, NPI 52, NPI 60, NPI 66, NPI 72, NPI 73, NPI 74, NPI 75, NPI 76m, NPI 77;
- α-1-antitrypsin: NPI 1, NPI 42, NPI 43, NPI 44, NPI 59;
- α-1-β glycoprotein: NPI 2, NPI 3, NPI 31, NPI 48;
- Antithrombin-III: NPI 4;
- Apo A-I: NPI 5, NPI 6, NPI 7, NPI 37, NPI 69, NPI 70, NPI 71;
- Apo A-IV: NPI 8, NPI 9, NPI 10;
- Apo J: NPI 12, NPI 13, NPI 14, NPI 15, NPI 16;
- Gelsolin: NPI 17;
- Haptoglobin: NPI 18;
- Hemopexin: NPI 19, NPI 20;
- Ig α-1 chain C region (heavy): NPI 21, NPI 22;
- Kininogen: NPI 23;
- Prostaglandin-H2 D-isomerase: NPI 24, NPI 25;
- Transthyretin: NPI 26, NPI 27, NPI 28m;
- Vitamin D-binding protein: NPI 29, NPI 30;
- Zn-α-2-glycoprotein: NPI 33;
- NPI 32, NPI 36, NPI 38, NPI 39, NPI 40, NPI 45, NPI 46, NPI 47, NPI 49, NPI 50, NPI 51, NPI 53, NPI 54, NPI 55, NPI 56, NPI 57, NPI 58, NPI 61, NPI 62, NPI 63, NPI 64, NPI 65, NPI 67, NPI 68.

20. An antibody capable of specifically recognizing one of the following protein isoforms associated with Alzheimer's disease, frontotemporal dementia, dementia with Lewy bodies, vascular dementia and/or depression:

- Apo E: NPI 11, NPI 34, NPI 35, NPI 41, NPI 52, NPI 60, NPI 66, NPI 72, NPI 73, NPI 74, NPI 75, NPI 76m, NPI 77;
- α-1-antitrypsin: NPI 1, NPI 42, NPI 43, NPI 44, NPI 59;

- α-1-β glycoprotein: NPI 2, NPI 3, NPI 31, NPI 48;
- Antithrombin-III: NPI 4;
- Apo A-I: NPI 5, NPI 6, NPI 7, NPI 37, NPI 69, NPI 70, NPI 71;
- Apo A-IV: NPI 8, NPI 9, NPI 10;
- Apo J: NPI 12, NPI 13, NPI 14, NPI 15, NPI 16;
- Gelsolin: NPI 17;
- Haptoglobin: NPI 18;
- Hemopexin: NPI 19, NPI 20;
- Ig α-1 chain C region (heavy): NPI 21, NPI 22;
- Kininogen: NPI 23;
- Prostaglandin-H2 D-isomerase: NPI 24, NPI 25;
- Transthyretin: NPI 26, NPI 27, NPI 28m;
- Vitamin D-binding protein: NPI 29, NPI 30;
- Zn-α-2-glycoprotein: NPI 33;
- NPI 32, NPI 36, NPI 38, NPI 39, NPI 40, NPI 45, NPI 46, NPI 47, NPI 49, NPI 50, NPI 51, NPI 53, NPI 54, NPI 55, NPI 56, NPI 57, NPI 58, NPI 61, NPI 62, NPI 63, NPI 64, NPI 65, NPI 67, NPI 68.

21. A kit comprising an antibody according to claim 20.

22. An antibody according to claim 20 or a kit according to claim 21 for use in the screening, diagnosis or prognosis in a mammal of Alzheimer's disease, frontotemporal dementia, dementia with Lewy bodies, vascular dementia and/or depression, for identifying a mammal at risk of developing Alzheimer's disease, frontotemporal dementia, dementia with Lewy bodies, vascular dementia and/or depression, or for monitoring the effect of therapy administered to a mammal having Alzheimer's disease, frontotemporal dementia, dementia with Lewy bodies, vascular dementia and/or depression.

23. An antibody according to claim 20 or a kit according to claim 21 for use in the differential diagnosis in a mammal of Alzheimer's disease, frontotemporal dementia, dementia with Lewy bodies, vascular dementia and/or depression.

24. Use of an antibody according to claim 20 for the preparation of a kit for the screening, diagnosis or prognosis in a mammal of Alzheimer's disease, frontotemporal dementia, dementia with Lewy bodies, vascular dementia and/or depression, for identifying a mammal at risk of developing Alzheimer's disease, frontotemporal dementia, dementia with Lewy bodies, vascular dementia and/or depression, or for monitoring the effect of therapy administered to a mammal having Alzheimer's disease, frontotemporal dementia, dementia with Lewy bodies, vascular dementia and/or depression.

25. Use of an antibody according to claim 20 for the preparation of a kit for the differential diagnosis in a mammal of Alzheimer's disease, frontotemporal dementia, dementia with Lewy bodies, vascular dementia and/or of depression.

26. A method of screening for agents that interact with and/or modulate the expression or activity of a protein or protein isoform according to claim 16, said method comprising:

(a) contacting said protein or protein isoform or a portion of said protein or protein isoform with said agent; and

(b) determining whether or not said agent interacts with and/or modulates the expression of said protein or protein isoform or said portion of the protein or protein isoform.